Consensus on the management of intracranial germ-cell tumours

Matthew J Murray, Ute Bartels*, Ryo Nishikawa, Jason Fangusaro, Masao Matsutani†, James C Nicholson†*

The management of intracranial germ-cell tumours is complex because of varied clinical presentations, tumour sites, treatments and outcomes, and the need for multidisciplinary input. Participants of the 2013 Third International CNS Germ Cell Tumour Symposium (Cambridge, UK) agreed to undertake a multidisciplinary Delphi process to identify consensus in the clinical management of intracranial germ-cell tumours. 77 delegates from the symposium were selected as suitable experts in the field and were invited to participate in the Delphi survey, of which 64 (83%) responded to the invitation. Invited participants represented multiple disciplines from Asia, Australasia, Europe, and the Americas. 38 consensus statements encompassing aspects of intracranial germ-cell tumour work-up, staging, treatment, and follow-up were prepared. To achieve consensus, statements required at least 70% agreement from at least 60% of respondents. Overall, 34 (89%) of 38 statements met consensus criteria. This international Delphi approach has defined key areas of consensus that will help guide and streamline clinical management of patients with intracranial germ-cell tumours. Additionally, the Delphi approach identified areas of different understanding and clinical practice internationally in the management of these tumours, areas which should be the focus of future collaborative studies. Such efforts should translate into improved patient outcomes.

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*Joint first authors

†Joint senior authors

Department of Paediatric Haematology and Oncology, Cambridge University Hospitals NHS Trust, Cambridge, UK (M J Murray PhD, J C Nicholson DM)**; Pediatric Brain Tumour Program, Hospital for Sick Children, Toronto, ON, Canada** (U Bartels MD)**; Department of Neuro-Oncology/ Neurosurgery, Saitama Medical University International Medical Centre, Hidaka, Japan** (Prof R Nishikawa MD, Prof M Matsutani MD)**; and Department of Pediatric Hematology/Oncology, Neuro-Oncology and Stem Cell Transplantation, Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL, USA** (J Fangusaro MD)

Correspondence to:
Dr James Nicholson, Department of Paediatric Haematology and Oncology, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK
james.nicholson@addenbrookes.nhs.uk

Introduction

Intracranial germ-cell tumours represent a rare and histologically heterogeneous group of predominantly midline neoplasms. Incidence varies substantially across the continents, with North American (Surveillance, Epidemiology, and End Results Program for Central Brain Tumor Registry of the United States) and international (International Agency for Research on Cancer) data[1] showing overall incidence of 0·6 per million per year in the USA, 1·0 per million per year in Europe, and 2·7 per million per year in Japan.[2] The classification systems and terminology used to describe intracranial germ-cell tumours is controversial. Histologically, these tumours are often segregated into three groups—namely, pure germinoma, teratoma, and non-germinomatous germ-cell tumours. Non-germinomatous germ-cell tumours are often mixed tumours and can be composed of any combination of yolk sac tumour, embryonal carcinoma, and choriocarcinoma.[2] Confusingly, non-germinomatous germ-cell tumours can also contain germinoma or teratoma, or both, which challenges some classification systems.

Diagnostic methods also vary, with some countries relying on surgical (ie, histological) verification for diagnosis upfront, often with a gross total resection rather than taking a biopsy.[2] In other countries, germ-cell tumours are not diagnosed with primary surgery but on the basis of raised tumour markers in the presence of consistent radiological appearances. The tumour markers used for this purpose are α-fetoprotein (typically raised in the presence of yolk sac tumour) and human chorionic gonadotropin (HCG; typically raised in the presence of choriocarcinoma). An increase in α-fetoprotein or HCG to greater than a defined threshold in either the serum or cerebrospinal fluid is taken to suggest the presence of these specific malignant components, and confirms the diagnosis of a so-called secreting non-germinomatous germ-cell tumour. On the basis of experience from previous clinical studies, however, marker thresholds vary across continents. Surgical biopsy is reserved for patients who are marker-negative—in other words, patients who do not have serum or cerebrospinal fluid concentrations of α-fetoprotein or HCG greater than the defined threshold.[2]

Classification systems for intracranial germ-cell tumours reflect the excellent overall survival for patients with germinoma and the inferior survival for those with non-germinomatous germ-cell tumours. Three risk groups are identified in Japanese treatment stratifications—pure germinoma, intermediate-prognosis intracranial germ-cell tumours, and poor-prognosis tumours, with the latter two groups comprising mixed malignant non-germinomatous germ-cell tumours.[3] Historically, in Europe and the Americas, two risk groups were identified (germinoma and non-germinomatous germ-cell tumours). More recently, patients in Europe with diagnostic serum or cerebrospinal fluid α-fetoprotein concentrations of more than 1000 kU/L have been identified as a high-risk non-germinomatous germ-cell tumour group,[4] for which the benefit of treatment intensification is being tested at present. Final results of the Children's Oncology Group Non-Germinomatous Germ Cell Tumour Trial (ACNS 0122),[5] which included children from North America and Australia, are due to be reported imminently.

Unsurprisingly, in view of these differing diagnostic and classification approaches, the evolution of treatment by neurosurgeons, radiation oncologists, and medical or paediatric oncologists has resulted in diverse treatment strategies in the management of these patients.[2] Principles of treatment include radiotherapy in all cases of germinoma and non-germinomatous germ-cell tumour to achieve good patient outcomes, except in infants and very young children where a chemotherapy-only approach is often attempted to avoid the devastating long-term

sequelae of radiotherapy. In view of inferior survival in patients with non-germinomatous germ-cell tumours (compared with pure germinoma), higher radiotherapy doses have to be used with less scope for dose reductions than possible for germinoma tumour treatment.[2] Chemotherapy has been used for the treatment of both germinoma and non-germinomatous germ-cell tumours, helping to reduce radiotherapy fields or doses, or both, during germinoma treatment by some research groups, with an aim to reduce or spare the late-effects of treatment.[2] Generally, the mainstay of treatment for teratoma without malignant transformation is surgery, which is curative for most patients if a gross total resection can be achieved.[2]

As a consequence of these complexities, which can include the relative difficulty of surgical access to the tumour site, the absence of diagnostic markers for specific tumour types, variable patient responses to both chemotherapy and radiotherapy, and the frequent presence of endocrine complications, optimum management of patients with intracranial germ-cell tumours necessitates the input of experts from multiple disciplines to form a collaborative approach to care.[2]

Additionally, the paucity of intracranial germ-cell tumour specimens available for molecular analysis has hampered the understanding of the pathogenesis of intracranial germ-cell tumours. This issue was addressed by the formation of consortia that facilitated the publication of key biological findings in 2014.[6,7] In the future, the aim will be to incorporate molecular markers into intracranial germ-cell tumour clinical trials to assist diagnosis and inform prognostic and treatment strategies.[2]

As a result of these challenges, three international symposia have now been held between 2003 and 2013, focusing specifically on the clinical management of intracranial germ-cell tumours, with a fourth symposium that was held in Tokyo in 2015. The first symposium was held in Kyoto, Japan, in 2003, followed by a second in Los Angeles, USA, in 2005.[2] Several key controversies in the management of intracranial germ-cell tumours were discussed during these meetings. Outputs from these early symposia, for example, included the reporting of surgical management guidelines.[8] The aims of the third symposium, held in Cambridge, UK, in 2013, were to further increase the clinical and biological understanding of intracranial germ-cell tumours, to overcome management differences where necessary, and to reach consensus where possible.[2] In total, 117 delegates attended from 25 countries across five continents, representing the multidisciplinary specialties involved in the clinical management of intracranial germ-cell tumours. From these initial discussions a committee was formed, which developed Delphi consensus statements[9,10] covering wide-ranging aspects of the clinical management of intracranial germ-cell tumours. These statements were subsequently subjected to online voting using a web-based survey by representative selected experts who attended the third symposium. This Review describes the results (panel) of this multidisciplinary Delphi method and the challenges that remain in the management of patients with intracranial germ-cell tumours.

Methods

Possible areas for international consensus were examined in a preliminary discussion at the Third International CNS Germ Cell Tumour Symposium on April 17–20, 2013, in Cambridge, UK. 117 delegates attended from five continents, including invited recognised experts in the field and those experts who had submitted abstracts to the symposium. Attendees agreed that Delphi consensus statements[10] would subsequently be drafted. A representative committee of six individuals representing Asia, the Americas, and Europe was responsible for this process (MJM [UK], UB [Canada], RN [Japan], JF [USA], MM [Japan], and JCN [UK]).

The figure provides details of the consensus process. Of the 117 symposium delegates, 77 recognised experts in their respective national or international groups were invited to participate in the Delphi process. 31 were from Europe (40%), 26 from Asia (34%), and 20 from the Americas (26%). 64 (83%) experts accepted the invitation (25 Europe [39%], 23 Asia [36%], and 16 from the Americas [25%]); this figure was set as the initial denominator for subsequent Delphi voting. 38 consensus statements encompassing various aspects of intracranial germ-cell tumour work-up, staging, treatment, and follow-up were prepared by the Delphi committee between December, 2013, and June, 2014, by use of the Delphi consensus methods.[10] Voting and responses were collated using a web-based survey. The statements were distributed for a first round of voting between October, 2014, and November, 2014. Participants were asked to rate every statement with four possible responses: "I support the statement"; "I would support the statement with modification"; "I do not support the statement" (as described[11]); or "I do not have the experience in this area to be able to comment". If respondents selected the last response, their vote did not count towards the denominator (ie, the total number of responses recorded for that statement). Additionally, a free text comments section was included below each statement to allow for suggested modifications. If a participant did not wholly agree with the statement, they were strongly encouraged to make comments to explain their rationale. If at least 70% of votes were in support of a statement from at least 60% of participants in each round of voting, the statement was accepted.[11] Where less than 70% consensus occurred, statements were revised on the basis of respondents' comments and redistributed in a second and final round of voting between November, 2014, and December, 2014. Accepted statements are listed in the panel. The rejection of unsuccessful statements is summarised in the Discussion; the statements that did